

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

Eric S. Rosenberg, M.D., *Editor*
 Jo-Anne O. Shepard, M.D., *Associate Editor*
 Sally H. Ebeling, *Assistant Editor*

Nancy Lee Harris, M.D., *Editor*
 Alice M. Cort, M.D., *Associate Editor*
 Emily K. McDonald, *Assistant Editor*



Case 30-2014: A 29-Year-Old Man with Diarrhea, Nausea, and Weight Loss

Daniel P. Hunt, M.D., Dushyant V. Sahani, M.D., Kathleen E. Corey, M.D., M.P.H.,
and Ricard Masia, M.D., Ph.D.

PRESENTATION OF CASE

From the Departments of Medicine (D.P.H.), Radiology (D.V.S.), Gastroenterology (K.E.C.), and Pathology (R.M.), Massachusetts General Hospital, and the Departments of Medicine (D.P.H.), Radiology (D.V.S.), Gastroenterology (K.E.C.), and Pathology (R.M.), Harvard Medical School — both in Boston.

N Engl J Med 2014;371:1238-47.

DOI: 10.1056/NEJMcpc1405218

Copyright © 2014 Massachusetts Medical Society.

Dr. Daniel L. Motola (Gastroenterology): A 29-year-old man was seen in the walk-in clinic at this hospital because of diarrhea and weight loss.

The patient had been well until 1 year before the current presentation, when diarrhea with loose, unformed stools developed; the diarrhea occurred up to six times per day and was associated with urgency and mild abdominal discomfort. During the 4 months before this presentation, unintentional weight loss of approximately 10 kg occurred and increasing fatigue developed. He had had no fevers, and the symptoms did not worsen after he ate dairy or wheat products. He had a history of asthma and had had excision of a congenital nevus and inguinal herniorrhaphy in the past. He took no medications and was allergic to penicillin. He was of Italian and Chinese ancestry. He had no known exposure to sexually transmitted diseases or hepatitis. He was single and worked in a retail store. His late grandfather had had hypertension, and his late father had had diabetes mellitus, thyroid disease, nephrolithiasis, rheumatoid arthritis, asthma, and hypertension; his brother and half siblings were healthy.

On examination, the blood pressure was 147/102 mm Hg, the pulse 80 beats per minute, and the temperature 36.8°C. The remainder of the examination was normal. The hematocrit, hemoglobin level, platelet count, erythrocyte sedimentation rate, and results of renal-function tests were normal, as were blood levels of vitamin B₁₂, folic acid, electrolytes, calcium, magnesium, glucose, glycated hemoglobin, total protein, albumin, globulin, and free thyroxine (T₄); other test results are shown in Table 1. Testing for the human immunodeficiency virus antibody and p24 antigen was negative, as was serologic testing for celiac disease.

After the test results were received, the patient was called and was asked to return to the outpatient clinic the next day. On examination, the blood pressure was 156/91 mm Hg, the pulse was 80 beats per minute, and the temperature was normal. The remainder of the examination was unchanged. Testing for hepatitis B virus (HBV) surface antibody was positive, and testing for HBV surface antigen, core antibody, e antigen, and e antibody was negative, as was testing for hepatitis C virus (HCV) antibody. Other test results are shown in Table 1. Examination of

the stool for ova and parasites was negative, and stool cultures showed normal enteric flora and no enteric pathogens. An appointment in the gastroenterology clinic was scheduled. Three days after his first presentation, the patient noted increasing nausea and returned to the outpatient clinic.

Dr. Dushyant V. Sahani: During that visit, color Doppler ultrasonography of the abdomen revealed mild splenic enlargement, with the spleen measuring 14.3 cm in length (normal length, ≤ 12 cm). The liver was normal in size and echotexture. The liver vasculature (including the portal vein, hepatic veins, and vena cava) was patent and had a normal flow pattern (Fig. 1). There was no free fluid in the abdomen.

Dr. Motola: On follow-up evaluation in the gastroenterology clinic, 3 weeks after the patient's initial presentation, he reported recent early satiety and "reddish" stools (with no frank blood). He reported dry skin but no pruritus, fevers, rash, oral ulcers, joint pains, or skin lesions other than multiple nevi. He had traveled to an island off the coast of New England 10 months earlier but did not recall having any tick bites. There was no family history of liver disease or inflammatory bowel disease.

On examination, the vital signs were normal. The weight was 85.3 kg, the height 190.5 cm, and the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) 23.5. The remainder of the examination was normal. Testing for mutations associated with hereditary hemochromatosis (H63D and C282Y) was negative. Three weeks later, esophagogastroduodenoscopy revealed grade I varices in the lower third of the esophagus; the results were otherwise normal. Colonoscopic examination revealed normal mucosa. Random biopsies of the stomach, small bowel, and colon were performed, after which more bleeding occurred than expected. Pathological examination of the biopsy specimens revealed normal mucosa. Additional laboratory test results are shown in Table 1.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Daniel P. Hunt: Diarrhea developed in this young man about a year before he sought medical attention. During the 4 months before his first

evaluation, he began to have fatigue in addition to the diarrhea and subsequently lost 10 kg. It would be helpful to ask additional questions before pursuing costly tests, in order to better understand this patient's illness and to refine the differential diagnosis. Why did the patient first seek medical attention a year after the onset of symptoms? Was there a reason for the delay? Did he feel depressed? Had he previously consulted with a physician about these symptoms?

CHRONIC DIARRHEA

It might be useful to better characterize the diarrhea.¹ For example, what is the consistency and color of the stools? Has the diarrhea alternated with constipation? Does the diarrhea occur during the night? Has he had incontinence? What does he think might be causing or contributing to the diarrhea?

There is an extensive differential diagnosis for chronic diarrhea.² Guidelines suggest that the initial evaluation should include a complete blood count, iron studies, a serologic test for celiac disease, and tests of liver function, thyroid function, the serum calcium level, and the vitamin B₁₂ level.³ This patient underwent a far more extensive evaluation, but among the results of the recommended initial studies, the elevated hepatic aminotransferase levels and bilirubin levels redirect attention to his liver and suggest that he has some type of chronic hepatitis. In addition, the mildly elevated prothrombin time suggests impairment of liver function and raises the possibility of cirrhosis. Splenomegaly and the somewhat unexpected finding of esophageal varices suggest portal hypertension, most likely as a consequence of cirrhosis.

LIVER DISEASE AND CIRRHOSIS

Common causes of cirrhosis include chronic alcohol use, viral hepatitis (either HBV or HCV), non-alcoholic steatohepatitis, and hereditary hemochromatosis.⁴ The patient does not consume alcohol. Evaluation of serologic markers for hepatitis indicates previous exposure to or immunization for HBV but no ongoing infection. He does not have HCV. We cannot rule out nonalcoholic steatohepatitis on the basis of the available evidence, but his current BMI is normal and there is no history of obesity. The elevated ferritin level raises the possibility of hereditary hemochromatosis, but the mutations H63D and C282Y were

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation	1 Day after Presentation, Outpatient Clinic	3 Wk after Presentation, Gastroenterology Clinic	6 Wk after Presentation	6.5 Wk after Presentation
White-cell count (per mm ³)	4500–11,000	10,300	8200	7400		7800
Differential count (%)						
Neutrophils	40–70	60.6	64.3	52.1		53.4
Lymphocytes	22–44	17.4	16.3	24.4		30.1
Monocytes	4–11	10.7	8.3	10.8		8.4
Eosinophils	0–8	8.9	9.1	10.7		6.8
Basophils	0–3	2.0	1.6	1.6		1.2
Activated partial-thromboplastin time (sec)	22.0–35.0				49.1	44.6
Prothrombin time (sec)	11.0–14.0				17.7	16.8
International normalized ratio	0.9–1.1				1.5	1.4
Globulin (g/dl)	2.3–4.1	3.9	3.5	4.2	4.0	4.7
Bilirubin (mg/dl)						
Total	0.0–1.0	1.7	2.0	1.4	2.8	1.6
Direct	0.0–0.4		0.8	0.4	1.1	0.6
Alkaline phosphatase (U/liter)	45–115	111	102	98	68	114
Alanine aminotransferase (U/liter)	10–55	180	176	131	142	132
Aspartate aminotransferase (U/liter)	10–40	167	172	154	167	143
Phosphorus (mg/dl)	2.6–4.5	1.4				
Thyrotropin (μU/ml)	0.40–5.00	9.17	4.86			
Ferritin (ng/ml)	30–300		1716	1677		
Iron (μg/dl)	45–160		134	109		
Iron-binding capacity (μg/dl)	230–404		Unable to perform test	142		
Antinuclear antibody	Negative at 1:40 and 1:160 dilutions		Positive at 1:40 dilu- tion, speckled pattern; negative at 1:80 and 1:160 dilutions			
Immunoglobulin (mg/dl)						
IgA	69–309	389		467		
IgG	614–1295			2559		
IgM	53–334			242		

Serum protein electrophoresis	Normal pattern
Smooth-muscle antibody	Positive at 1:20 dilution
Antimitochondrial antibody	Negative at 1:20 dilution
α_1 -Antitrypsin (mg/dl)	240
Free kappa light chain (mg/liter)	40.4
Free lambda light chain (mg/liter)	60.7
Ratio of free kappa light chain to free lambda light chain	0.7

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

not identified. Furthermore, elevated ferritin levels, even above 1000 ng per milliliter, are seen in several liver diseases besides hemochromatosis.^{5,6}

Since the common causes of chronic hepatitis and cirrhosis seem unlikely in this case, we should next consider less common causes, including α_1 -antitrypsin deficiency, autoimmune hepatitis, Wilson's disease, primary biliary cirrhosis, and drug or medication use. An α_1 -antitrypsin deficiency is ruled out because the α_1 -antitrypsin level exceeds the normal range. The negative test for antimitochondrial antibody argues against primary biliary cirrhosis. There is no history of drug or medication use. Could the patient have autoimmune hepatitis or Wilson's disease?

AUTOIMMUNE HEPATITIS

Patients with autoimmune hepatitis may present with fatigue, lethargy, anorexia, nausea, abdominal pain, itching, and arthralgia of small joints.⁷ Diarrhea is not a common symptom of this illness. The International Autoimmune Hepatitis Group proposed a scoring system intended to help estimate the probability of this illness (Table 2). This patient has a ratio of alkaline phosphatase to aspartate aminotransferase of less than 1.5 (+2 points in the scoring system), an IgG level that is 1.98 times as high as the normal level (+2 points), an antinuclear antibody titer of 1:40 (+1 point), negative viral tests (+3 points), no history of drug use (+1 point), and no history of substantial alcohol use (+2 points). The other components of the scoring system, including results of a liver biopsy and response to treatment, are not yet known for this patient. A total score of 11 points in this system suggests that autoimmune hepatitis is the probable but not definite diagnosis.

The presence of eosinophilia has been associated with autoimmune hepatitis.^{10,11} Also, an elevated ferritin level may occur with autoimmune hepatitis.¹² Autoimmune hepatitis occurs in Italian and Chinese populations.¹³⁻¹⁵ Autoimmune disorders are common among first-degree relatives of children with autoimmune hepatitis in a large case series.¹⁶

WILSON'S DISEASE

The American Association for the Study of Liver Diseases guidelines caution that Wilson's disease should be ruled out before a diagnosis of autoimmune hepatitis is made.⁸ I find it curious that a ceruloplasmin level is not included among the



Figure 1. Abdominal Ultrasound Image.

An image obtained during a color Doppler ultrasound examination of the abdomen shows normal liver echotexture and a patent portal vein.

values reported in the case history. Patients with Wilson's disease present with a range of hepatic manifestations, including persistently elevated serum aminotransferase levels, chronic hepatitis, cirrhosis, or fulminant hepatic failure.¹⁷ I normally consider Wilson's disease in the differential diagnosis when there is coexisting liver disease and a neuropsychiatric disorder. This patient was not noted to have any neurologic abnormalities or psychiatric illnesses. However, what caused him to tolerate 1 year of diarrhea and 4 months of progressive weight loss before seeking medical attention?

Criteria for the diagnosis of Wilson's disease are included in Table 2. Unfortunately, we do not have all the results necessary to use the Leipzig criteria, but these criteria suggest a number of other studies that might be considered for this patient, including a neuropsychiatric examination, an ophthalmologic slit-lamp examination for Kayser–Fleischer rings, and a serum ceruloplasmin test. A 2008 guideline for the diagnosis and management of Wilson's disease suggests that a diagnosis of Wilson's disease can be established by the presence of Kayser–Fleischer rings, a ceruloplasmin level of less than 20 mg per deciliter, and a 24-hour urinary copper level of greater than 40 μ g.¹⁸ A liver biopsy is the next study that should be performed in patients in whom the diagnosis is being considered. I think we can safely say that the diagnostic procedure for this patient was a liver biopsy, because it would be essential in establishing the diagnosis of either autoimmune hepatitis or Wilson's disease.

Are there other aspects of this patient's presentation that are consistent with Wilson's disease? The hypophosphatemia is unexplained, but Wilson's disease has been associated with Fanconi's syndrome, which could potentially lead to this finding.¹⁹ Although I am still troubled by the patient's chronic diarrhea, this symptom has been reported in children diagnosed with Wilson's disease.²⁰

Could this patient have coexisting autoimmune hepatitis and Wilson's disease, which have been reported in several patients?^{9,21,22} In a small case series comparing 33 patients with Wilson's disease alone with 9 patients with Wilson's disease and concurrent liver disease (including 4 patients with autoimmune hepatitis), the alkaline phosphatase level was substantially higher than normal in patients with concurrent liver disease.⁹ This patient has a normal alkaline phosphatase level, which argues against coexisting processes and leads me to believe that Wilson's disease alone is the most likely diagnosis.

Dr. Eric S. Rosenberg (Pathology): Dr. Motola, what was your impression when you initially examined this patient?

Dr. Motola: We initially focused our differential diagnosis on the abnormal results of liver-function tests and the bloody diarrhea. Although we considered primary sclerosing cholangitis and ulcerative colitis, we thought these would be unlikely given the patient's normal alkaline phosphatase level. We also considered hemochromatosis, Wilson's disease, and autoimmune hepatitis. To investigate the cause of the diarrhea, we elected to perform upper and lower endoscopies, which revealed grade I varices in the esophagus; all biopsy specimens were normal. Finally, we recommended that he undergo a 24-hour urine test for copper and a liver biopsy.

CLINICAL DIAGNOSIS

Wilson's disease or autoimmune hepatitis.

DR. DANIEL P. HUNT'S DIAGNOSIS

Wilson's disease.

PATHOLOGY

Dr. Ricard Masia: A transjugular liver biopsy was performed and revealed established cirrhosis, characterized by diffuse bridging fibrosis and nodu-

Table 2. Scoring Systems to Differentiate Autoimmune Hepatitis from Wilson's Disease.*

Criteria for Autoimmune Hepatitis†	Points	Criteria for Wilson's Disease‡	Points
Female sex	+2	Presence of Kayser–Fleischer rings	+2
Ratio of alkaline phosphatase to aspartate aminotransferase		Presence of neuropsychiatric symptoms suggestive of Wilson's disease	+2
>3	–2	Negative Coombs' test for hemolytic anemia (plus high serum copper level)	+1
<1.5	+2	24-Hr urinary copper level (in the absence of acute hepatitis)	
Gamma globulin or IgG level		Normal	0
>2.0 mg/dl above the ULN	+3	1–2 times the ULN	+1
1.5–2.0 mg/dl above the ULN	+2	>2 times the ULN	+2
1.0–<1.5 mg/dl above the ULN	+1	Normal, but 5 times the ULN after the administration of penicillamine	+2
<1.0 mg/dl above the ULN	0	Copper quantitation in the liver	
Antinuclear antibody, smooth-muscle antibody, or anti–liver–kidney microsome type 1 antibody titer		Normal	–1
>1:80	+3	≤5 times the ULN	+1
1:80	+2	>5 times the ULN	+2
1:40	+1	Positive rhodanine stain for hepatocytes	+1
<1:40	0	Serum ceruloplasmin level	
Positive test for antimitochondrial antibody	–4	Normal	0
Viral hepatitis		10–20 mg/dl	+1
Positive	–3	<10 mg/dl	+2
Negative	+3	Mutation analysis	
Illicit-drug use		No mutation detected	0
Yes	–4	Disease-causing mutation on one chromosome	+1
No	+1	Disease-causing mutation on both chromosomes	+4
Alcohol use		Total score	
<25 g/day	+2	Wilson's disease highly likely	>3
>60 g/day	–2	Wilson's disease probable, investigate further	2–3
Presence of HLA-DR3 or HLA-DR4 allele	+1	Wilson's disease unlikely	0–1
Presence of immune disease (thyroiditis, colitis, or other)	+2		
Presence of antibody to soluble liver antigen, anti-actin antibody, anti–liver cytosol type 1 antibody, or perinuclear antineutrophil cytoplasmic antibody	+2		
Presence of histologic features			
Interface hepatitis	+3		
Plasmacytes	+1		
Rosettes	+1		
No interface hepatitis, plasmacytes, or rosettes	–5		
Biliary changes	–3		
Other features	–3		
Treatment response			
Complete	+2		
Relapse	+3		
Pretreatment aggregate score			
Definite diagnosis of autoimmune hepatitis	>15		
Probable diagnosis of autoimmune hepatitis	10–15		
Post-treatment aggregate score			
Definite diagnosis of autoimmune hepatitis	>17		
Probable diagnosis of autoimmune hepatitis	12–17		

* ULN denotes upper limit of the normal range.

† Data are adapted from Manns et al.⁸‡ For Wilson's disease, Leipzig criteria were used. Data are adapted from Wong et al.⁹

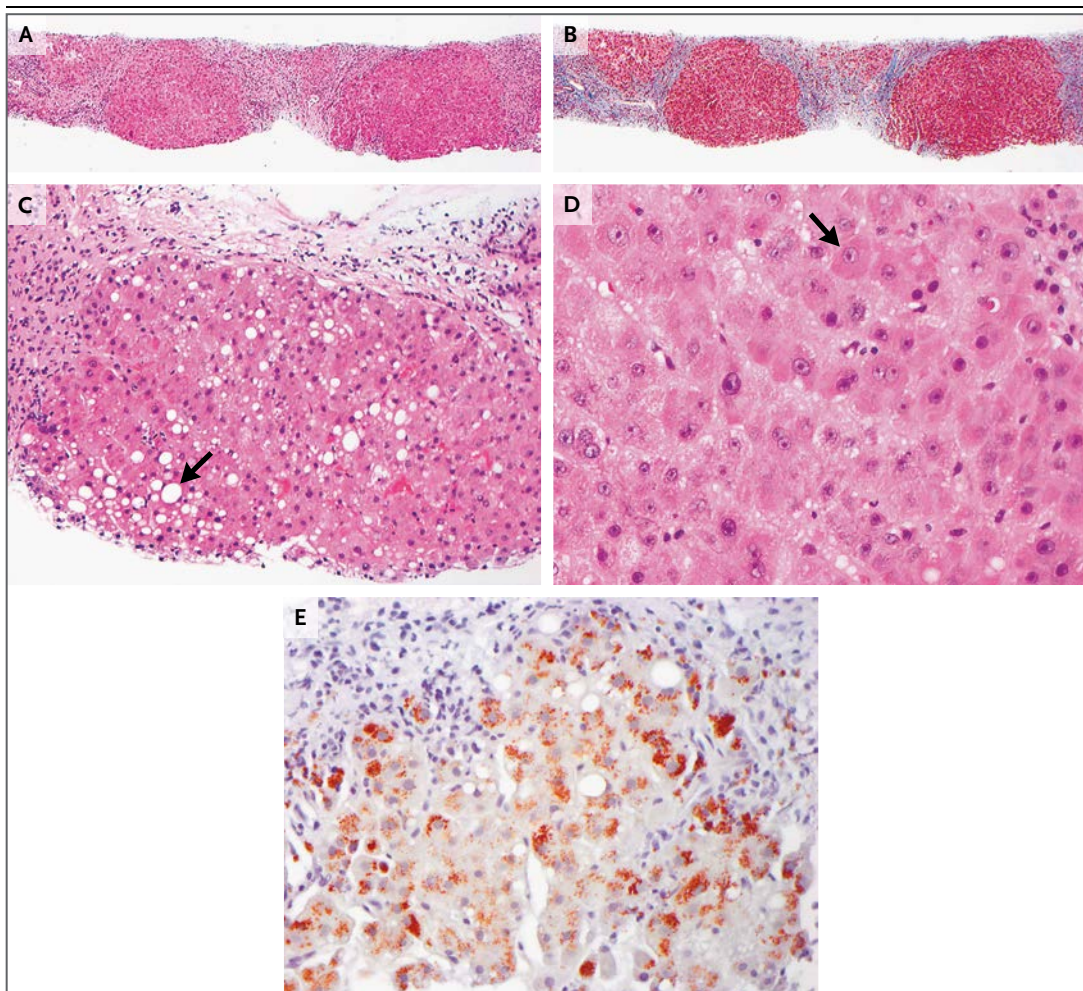


Figure 2. Liver-Biopsy Specimen.

A specimen obtained during a transjugular liver biopsy shows established cirrhosis, characterized by diffuse bridging fibrosis and nodularity (Panel A, hematoxylin and eosin; and Panel B, trichrome). Focal macrovesicular steatosis is also seen (Panel C, arrow; hematoxylin and eosin). Some hepatocytes are enlarged and contain abundant granular eosinophilic cytoplasm; these features (referred to as oncocytic change) are due to an increase in the size and number of mitochondria (Panel D, arrow; hematoxylin and eosin). Histochemical staining for copper shows extensive copper deposition in hepatocytes at the edge of cirrhotic nodules (Panel E, rhodanine) that is consistent with Wilson's disease.

larity (Fig. 2A and 2B). There was only mild mononuclear septal inflammation, with minimal interface activity. There was focal macrovesicular steatosis (Fig. 2C), with no hepatocyte ballooning. A trichrome stain highlighted areas of pericellular and perisinusoidal fibrosis. The presence of steatosis and pericellular fibrosis may indicate a previous steatohepatitis. In some areas, hepatocytes were enlarged and contained abundant granular eosinophilic cytoplasm; these fea-

tures (referred to as oncocytic change) are due to an increase in the size and number of mitochondria and are indicative of toxic-metabolic injury (Fig. 2D). All these features are nonspecific but can be seen in patients with genetic disorders of liver metabolism, such as Wilson's disease. Iron staining and periodic acid-Schiff staining with diastase digestion showed no hepatocytic iron or globules. However, a histochemical (rhodanine) stain for copper showed extensive copper deposi-

tion in hepatocytes at the edge of cirrhotic nodules (Fig. 2E). The copper granules ranged from fine to coarse and had a perinuclear distribution in some cells. These histopathologic findings are consistent with Wilson's disease. It is important to note that hepatocytic copper deposition in Wilson's disease may be uneven,²³ and needle biopsies are often associated with sampling error; therefore, histochemical staining may be unreliable and yield false negative results. In addition, the most commonly used stains (rhodanine and rubeanic acid) mainly detect copper concentrated in lysosomes, a finding that is seen in the late stages of the disease.²⁴ In the early stages, excess copper is diffusely distributed in the cytoplasm and is not detected by these stains. Thus, a negative histochemical stain for copper does not rule out the diagnosis of Wilson's disease.¹⁸

The most reliable diagnostic test for Wilson's disease is copper quantitation in tissue. In this case, copper quantitation in a sample of fresh tissue revealed a value of 1369 μg per gram of dry weight (reference range, 10 to 35). Values greater than 250 μg per gram of dry weight have 83.3% sensitivity and 98.6% specificity for Wilson's disease²⁵; this diagnostic threshold is incorporated into practice guidelines of the American Association for the Study of Liver Diseases.¹⁸ A value greater than 1000 μg per gram of dry weight, as was seen in this case, is considered virtually diagnostic of Wilson's disease.

DISCUSSION OF MANAGEMENT

Dr. Kathleen E. Corey: Management of Wilson's disease is determined by the clinical presentation of the patient. Asymptomatic patients, without signs of hepatic or neurologic disease, can be treated with zinc. Zinc acts in the enterocyte to induce metallothionein, an endogenous metal chelator. For patients with evidence of neurologic or hepatic involvement, chelation therapy with penicillamine or trientine is indicated. The choice of chelator is influenced by the presence of neurologic disease. Patients with neurologic manifestations who are initially treated with trientine have higher rates of neurologic deterioration than patients with neurologic manifestations who are initially treated with penicillamine²⁶; thus, penicillamine may be preferred in this group. However, penicillamine is associated with high rates of

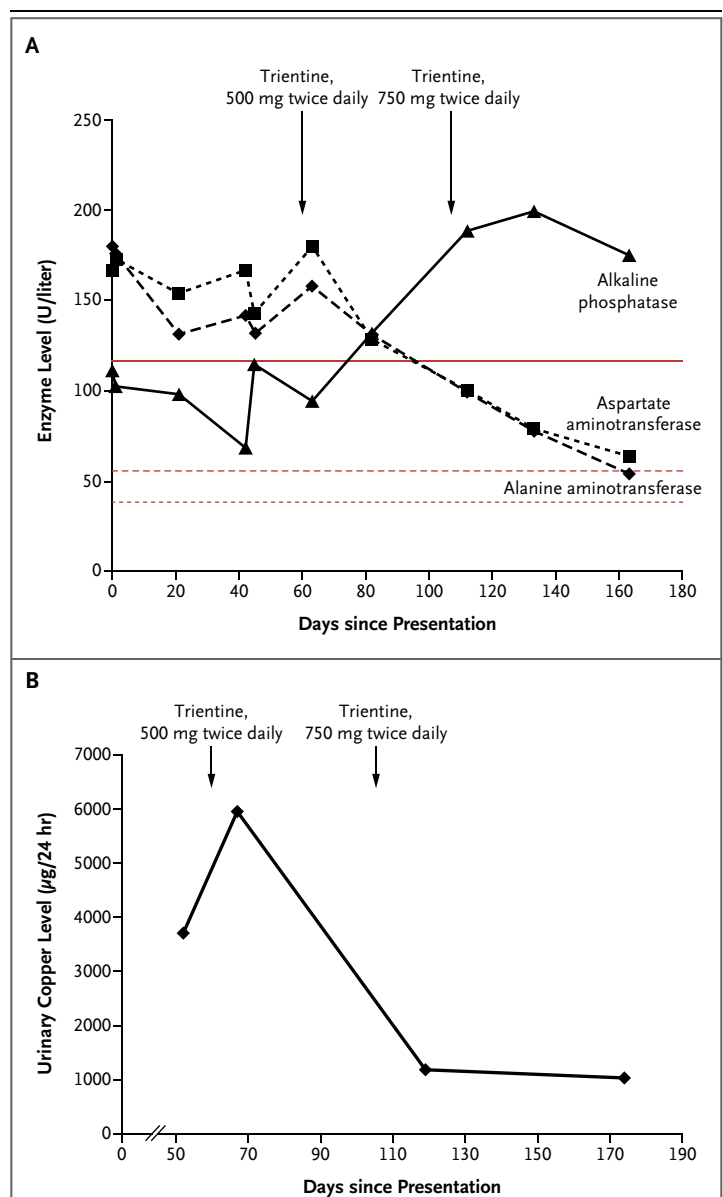


Figure 3. Enzyme Levels and 24-Hour Urinary Copper Levels before and after the Initiation of Trientine Therapy.

Before and after the initiation of trientine therapy, levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (Panel A) and the urinary copper level (Panel B) were measured. Red lines indicate the upper limit of the normal range for the respective enzyme.

adverse events leading to discontinuation of therapy, as compared with trientine.²⁶ Therefore, in patients without neurologic involvement, trientine is a reasonable initial therapy. For patients with decompensated liver disease that is unresponsive

to chelation therapy or for patients with fulminant hepatic failure, referral for evaluation for liver transplantation is warranted.²⁵ For this patient, who had no evidence of neurologic involvement, decompensated liver disease, or hepatic failure, chelator therapy with trientine was chosen.

FOLLOW-UP

Dr. Motola: In this patient, the administration of trientine was begun at a dose of 500 mg twice daily. We measured the 24-hour urinary copper levels before the initiation of therapy and at 2-month intervals thereafter. Two months after trientine therapy was begun, we increased the dose to 750 mg twice daily, which is the recommended maximum daily dose. The urinary copper levels initially increased and then steadily decreased as copper stores presumably were depleted. While the patient was receiving trientine, the blood levels of aspartate aminotransferase and alanine aminotransferase declined and the alkaline phosphatase level, which was initially normal, increased (Fig. 3). The alkaline phosphatase level is now above normal, and we think that we saw a normal level initially because copper was

interfering with the measurement of enzyme activity.

After treatment with trientine was begun, the diarrhea resolved. The patient has returned to work with increased energy and appetite and has regained approximately 5 kg.

Dr. Stephen Goldfinger (Gastroenterology): In the treatment of patients with Wilson's disease, do you restrict the diet to exclude foods containing high levels of copper, such as chocolate and liver?

Dr. Corey: Absolutely. This patient has been counseled on a low-copper diet and has subsequently eliminated those foods from his diet.

A Physician: How often do you see advanced cirrhosis in patients with normal imaging studies?

Dr. Corey: A large proportion of the patients in whom cirrhosis is suspected have normal imaging studies, especially patients with metabolic conditions.

PATHOLOGICAL DIAGNOSIS

Wilson's disease.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

- Camilleri M. Chronic diarrhea: a review on pathophysiology and management for the clinical gastroenterologist. *Clin Gastroenterol Hepatol* 2004;2:198-206.
- Juckett G, Trivedi R. Evaluation of chronic diarrhea. *Am Fam Physician* 2011;84:1119-26.
- Thomas PD, Forbes A, Green J, et al. Guidelines for the investigation of chronic diarrhoea, 2nd edition. *Gut* 2003;52:Suppl 5:v1-v15.
- Lefton HB, Rosa A, Cohen M. Diagnosis and epidemiology of cirrhosis. *Med Clin North Am* 2009;93:787-99.
- Lee MH, Means RT Jr. Extremely elevated serum ferritin levels in a university hospital: associated diseases and clinical significance. *Am J Med* 1995;98:566-71.
- Wong K, Adams PC. The diversity of liver diseases among outpatient referrals for an elevated serum ferritin. *Can J Gastroenterol* 2006;20:467-70.
- Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006;354:54-66.
- Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51:2193-213.
- Wong RJ, Gish R, Schilsky M, Frenette C. A clinical assessment of Wilson disease in patients with concurrent liver disease. *J Clin Gastroenterol* 2011;45:267-73.
- Chowdry S, Rubin E, Sass DA. Acute autoimmune hepatitis presenting with peripheral blood eosinophilia. *Ann Hepatol* 2012;11:559-63.
- Terrier B, Fontaine H, Schmitz J, et al. Coexistence and parallel evolution of hypereosinophilic syndrome, autoimmune hepatitis, and ulcerative colitis suggest common pathogenic features. *Am J Gastroenterol* 2007;102:1132-4.
- An IC, Tiwari AK, Ameda S, Laird-Fick HS. Autoimmune hepatitis: diagnostic dilemma in the setting of suspected iron overload. *Case Rep Gastrointest Med* 2013;2013:872987.
- Granito A, Muratori L, Pappas G, et al. Clinical features of type 1 autoimmune hepatitis in elderly Italian patients. *Aliment Pharmacol Ther* 2005;21:1273-7.
- Song GJ, Feng B, Rao HY, Wei L. Etiological features of cirrhosis inpatients in Beijing, China. *Chin Med J (Engl)* 2013;126:2430-4.
- Wang QX, Jiang WJ, Miao Q, et al. Clinical and histological features of autoantibody-negative autoimmune hepatitis in Chinese patients: a single center experience. *J Dig Dis* 2013;14:175-80.
- Gregorio GV, Portmann B, Reid F, et al. Autoimmune hepatitis in childhood: a 20-year experience. *Hepatology* 1997;25:541-7.
- Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. *Lancet* 2007;369:397-408.
- Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008;47:2089-111.
- Huster D. Wilson disease. *Best Pract Res Clin Gastroenterol* 2010;24:531-9.
- Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. *Liver Transpl* 2005;11:441-8.
- Milkiewicz P, Saksena S, Hubscher SG, Elias E. Wilson's disease with superimposed autoimmune features: report of two cases and review. *J Gastroenterol Hepatol* 2000;15:570-4.
- Yener S, Akarsu M, Karacanci C, et al. Wilson's disease with coexisting autoimmune hepatitis. *J Gastroenterol Hepatol* 2004;19:114-6.

23. Faa G, Nurchi V, Demelia L, et al. Uneven hepatic copper distribution in Wilson's disease. *J Hepatol* 1995;22:303-8.
24. Johncilla M, Mitchell KA. Pathology of the liver in copper overload. *Semin Liver Dis* 2011;31:239-44.
25. Ferenci P, Steindl-Munda P, Vogel W, et al. Diagnostic value of quantitative hepatic copper determination in patients with Wilson's disease. *Clin Gastroenterol Hepatol* 2005;3:811-8.
26. Weiss KH, Thurik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. *Clin Gastroenterol Hepatol* 2013;11:1028-35.

Copyright © 2014 Massachusetts Medical Society.

LANTERN SLIDES UPDATED: COMPLETE POWERPOINT SLIDE SETS FROM THE CLINICOPATHOLOGICAL CONFERENCES

Any reader of the *Journal* who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is now eligible to receive a complete set of PowerPoint slides, including digital images, with identifying legends, shown at the live Clinicopathological Conference (CPC) that is the basis of the Case Record. This slide set contains all of the images from the CPC, not only those published in the *Journal*. Radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs, as well as unpublished text slides, tables, and diagrams, are included. Every year 40 sets are produced, averaging 50-60 slides per set. Each set is supplied on a compact disc and is mailed to coincide with the publication of the Case Record.

The cost of an annual subscription is \$600, or individual sets may be purchased for \$50 each. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or e-mail Pathphotoslides@partners.org.